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EXAMINER
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ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/851,650	BARR ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-14,16 and 30-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-14,16 and 30-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (Paper No. 9, mailed on September 23, 2002), Applicants filed an election and amendment received on October 29, 2002 (Paper No. 10). Said amendment cancelled Claims 7, 15, and 17-29. Thus, Claims 1-6, 8-14, 16, and 30-39 are pending in the instant Office action.

Election

2. Applicants' election without traverse of Group I, Claims 1-6, 8-14, 16, and 30-39, in Paper No. 4 is acknowledged.

Priority

3. Applicants are granted the benefit of priority for the provisional application 60/033,193 filed on December 18, 1996, the non-provisional applications 08/989,332 filed in December 11, 1997 and 09/422,073 filed on October 21, 1999, and the international application PCT/US97/23014 filed on December 12, 1997 as requested in the transmittal sheet. The Examine notes that the PCT application was incorrectly noted under "foreign applications" while it is considered an internationally filed application which is filed in the U.S. The priority date granted for purposes of prior art is December 18, 1996.

Information Disclosure Statement

4. The information disclosure statement (Paper No. 7) filed on July 15, 2002 has been reviewed and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Drawings

5. The drawings have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Compliance with the Sequence Rules

6. By virtue of the amendment filed on August 24, 2000 (Paper No. 3), the instant application fully complies with the sequence rules.

Objections to the Specification

7. The specification is objected to for complete lacking continuity data in the first paragraph. In the transmittal sheet, the instant application claims the benefit of provisional application 60/033,193 filed on December 18, 1996, the non-provisional applications 08/989,332 filed in December 11, 1997 and 09/422,073 filed on October 21, 1999, and the international application PCT/US97/23014 filed on December 12, 1997; all these claims must be noted in the first paragraph along with appropriate status statement (abandoned, patented – USPN, pending). Appropriate amendment to the specification is required (see M.P.E.P. § 201.11).

8. The specification is objected to for not updating patent application number references throughout the specification:

a) On page 14, line 18, 08/675817 should be noted as USPN 6080555.

b) On page 25, line 18, and again on page 26, line 22, 08/238811 should be noted as USPN 5672491.

Appropriate correction is required.

9. The specification is objected to on the following confusing points:

a) On page 6, line 19, the abbreviation "gris" is not defined.

b) On page 20, line 19, "lac^{Iq} [?]" is wholly confusing; moreover, the [?] has been hand-crossed out.

Appropriate correction and/or clarification is required.

10. The specification is objected to for the following typographical errors:

a) On page 7, line 23, "phosphopantothenoylation" should be ---phosphopantotheinylation---; other corrections are required throughout the specification for the proper spelling of this term (pages 8, 18, 21, 24, and 27).

Appropriate correction is required.

Objections to the Claims

11. Claim 3 is objected to for lacking specific antecedent basis. The term "said PKS" should be ---said minimal PKS--- for particular antecedent basis

12. Claim 11 is objected to for lacking consistency. In step (c), the term "containing" should be ---comprising--- as found in the other steps of the claim. Correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claim 1 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The abbreviation "ACP" in line 3 must be defined upon its first appearance in the claims; the definition on line 5 is insufficient. Correction is required.

14. Claim 4 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In line 1, the antecedent basis of "the nucleotide sequence" is unclear since Claim 1 does not refer to a nucleotide sequence. Clarification is required.

15. Claims 8-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 8, lines 2 and 3, the antecedent basis of "said first vector" and "said second vector" is unclear since no first and second vectors are previously noted. Clarification is required.

16. Claim 10 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The "expression system for a cell-based detection system for a functional polyketide" is undefined by the specification and the prior art does not provide a basis to define this term, thus rendering Claim 10 unclear. Furthermore, Broach *et al.*, referred to in the instant specification, does not aid in establishing a definition. Clarification is required.

17. Claims 13-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 13, line 1, the antecedent basis of "said first and second

module" is unclear since neither Claim 8 nor Claim 12 refers to a first or second module. Clarification is required.

18. Claims 13 and 14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 13, the term "different" is unclear due to the copious amounts of mutagenesis and domain swapping found in the art of polyketide synthases. Applicants must define the word "different", for example, as "derived from polyketide synthases which produce different antibiotics". Clarification is required.

19. Claim 14 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The antecedent basis of "said nucleotide sequence encoding at least one module" is unclear because only in Claim 12 is a nucleotide sequence mentioned, and then only in reference to the second vector. Can either vector be considered an antecedent of this term? Clarification is required.

20. Claim 14 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The abbreviations "KR", "DH" and "ER" are not defined upon their first occurrence in the claims. Correction is required.

21. Claims 30-39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. In Claims 30 and 35, the term "functional polyketide synthase catalytic activity" is unclear. Polyketide synthases are multifunctional enzymes catalyzing a wide variety of reactions, for example an acyl transferase reaction. Must an antibiotic be produced? A polyketide? To claim a coding region of a catalytic activity is confusing. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

22. Claims 1-6, 16, 32, 34, 37, and 39 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are directed to host cells containing expression systems for polyketide synthases (PKSs) and holo acyl carrier protein (ACP) synthases where the claimed product is defined by its functional characteristics with respect to the ACP synthase component. In contrast to the copious amounts of structural and functional data on PKSs, wherein the name "polyketide synthase" dictates a particular structure and function, a holo ACP synthase is not defined in the instant specification, or in the art, other than by its ability to catalyze phosphopantetheinyl transfer to activate ACPs of PKSs.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, useful expression systems for holo ACP synthases are briefly described on pages 7-8 and 21-22 with functional characteristics and examples of *Bacillus brevis* gramicidin holo ACP synthase (GsP), *Bacillus subtilis* surfactin-related holo ACP synthase (sfp), and *E. coli* enterobactin synthetase holo ACP synthase (EntD). While these examples are offered, no structural homologies are defined so that the genus is structurally and functionally defined. Moreover, on page 21-22, *E. coli* fatty acid synthase holo ACP synthase (ACPS) does not function effectively. The difference between effective holo ACP synthases and those that are not effective at pantotheinylation of PKS systems is not structurally defined. Thus, the instant specification does not adequately describe, in both structural and functional terms, the proteins that meet the limitations of the term holo ACP synthase for use in the instant claims.

23. Claims 1-6, 16, 32, 34, 37, and 39 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for host cells containing expression systems for polyketide synthases (PKSs) and *particular* expression systems for holo acyl carrier protein (ACP) synthases, does not reasonably provide enablement for host cells containing expression systems for PKSs and *all* expression systems for holo ACP synthases. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims without undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the

breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In the instant specification, no guidance is presented for the purpose of determining expression systems for holo ACP synthases, i.e. determining genes encoding holo ACP synthases, with no discussion of homology among the holo ACP synthases used. The specification teaches three working examples of particular holo ACP synthases, namely, EntD from *E. coli*, GsP from *B. brevis*, and Sfp from *B. subtilis,* and demonstrate their utility as holo ACP synthases to catalyze a phosphopantetheinyl transfer reaction which converts apo-ACPs (inactive) to holo-ACPs (active) in the type I PKS, DEBS; similar data is also found in Lambalot *et al.* (1996) (see IDS). It is noted that using a holo ACP synthase from *E. coli*, ACPS, with a type I PKS producing erythromycin, DEBS, is not operable for the production of a holo ACP of DEBS. The art involving these holo ACP synthases is not well developed, and thus, the predictability of the art is very low.

Thus, applicants have enabled the use of expression systems using holo ACP synthases EntD, GsP, and Sfp to produce a holo ACPs of type I PKSs in *E. coli* host cells. Applicants have not enabled the use of these holo ACP synthases with type II PKSs. Furthermore, since not all holo ACP synthases will function with PKSs, noting the inoperable *E. coli* ACPS example, applicants have not enabled the use of other holo ACP synthases known at the time the invention was made unless the particular holo ACP synthase had further been shown to convert ACPs of particular PKSs. Applicants also have not enabled the identification of new holo ACP synthases.

24. Claim 4 is rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for cells containing expression systems for fusion protein comprising a fungal PKS and a holo ACP synthase, does not reasonably provide enablement for cells containing expression systems for fusion protein comprising a aromatic or modular PKSs and a holo ACP synthase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The Wands factors for ascertaining undue experimentation are described above.

The specification teaches a fusion protein of the fungal PKS 6-MSAS and the holo ACP synthase sfp (see Example 8). This fungal PKS is the simplest form of a PKS and does not necessarily correlated with aromatic or modular PKS systems. Aromatic and modular PKS are complex entities whose protein units form multi-protein complexes for their production catalytic function. The specification provides no working examples or guidance for the production of aromatic or modular PKS fusion protein systems. It is wholly unpredictable how to produce a functional fusion protein for these PKS systems. For these reasons, the instant claim is not enabled to the full extent of its scope.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

25. Claims 8, 9, 11, and 12 are rejected under 35 U.S.C. § 102(e) as being anticipated by Khosla *et al.* (USPN 5,712,146) (see IDS). The instant claims are drawn to actinomycete host cells having (1) at least three vectors, each vector comprising a portion of an aromatic PKS expression system or (2) at least two vectors, each vector comprising a module of a modular PKS expression system.

Khosla *et al.* (USPN 5,712,146) teach actinomycete host cells, *Streptomyces coelicolor* CH999, and their transformation with "one or more expression vectors ... in order to incorporate a random assortment of PKS genes, modules, active sites, or portions" (emphasis added) (see column 17, lines 45-50); said "random assortment" is "any combination and/or order of genes, homologs or mutants which encode for the various PKS enzymes, modules, active sites or portions thereof derived from aromatic, modular or fungal PKS gene clusters" (see column 10, lines 40-44). Khosla *et al.* (USPN 5,712,146) further teach that such "expression vectors will include control sequences operably linked to the desired PKS coding sequence", such control sequences including promoters (see column 17, lines 53-60), and said expression vector will also include selectable markers (see column 4, lines 45-59).

Khosla *et al.* (USPN 5,712,146) teach the various active sites of a modular polyketide synthase (PKS) gene as being ketosynthase (KS), acyl transferase (AT), and acyl carrier protein (ACP) active sites (see column 19, lines 14-20). Khosla *et al.* (USPN 5,712,146) also define a minimal aromatic PKS to include a ketosynthase/acyltransferase (KS/AT) active site, a chain-

length determining factor (CLF), and an acyl carrier protein (ACP) (see column 2, lines 25-30). These definitions, coupled with the "random assortment" of modular or aromatic PKS active sites on one or more expression vectors, anticipate Claims 11 and 12.

For inventions in the absence of modified chromosomes (i.e. separate vectors), teachings are expressly found in Khosla *et al.* (USPN 5,712,146) as the specification directs anyone of ordinary skill in the art at the time the invention was made to practice the invention since Khosla *et al.* (USPN 5,712,146) expressly identify the embodiments in their specification.

26. Claims 30-31 and 33 are rejected under 35 U.S.C. § 102(b) as being anticipated by Shen *et al.* (1993) (see IDS). The instant claims are drawn to yeast cells containing vectors encoding a selectable marker and an expression system for a functional aromatic PKS and methods of expressing the PKS protein.

Shen *et al.* (1993) teach the "*S. glaucescens* WMH1077/(pWHM722) transformant that carries the *tcmKLMN* genes under the control of a strong constitutive promoter in ... vector pIJ486" (see page 1536, left column, first full paragraph) and the culturing of said transformant to express the aromatic, type II polyketide synthase (PKS) *tcmKLMN* gene products; *S. glaucescens* is a yeast host cell. A selection marker is inherent in the expression plasmid for selection after transformation since selection of transformed cells cannot be performed in the absence of a selectable marker and post-transformation selection is essential to an effective transformation. Also, the *tcmKLMN* genes code for ketosynthase and acyl carrier protein PKS activities of the type II PKS producing tetracenomycin (see page 1535, right column, first paragraph).

27. Claims 30-31 and 33 are rejected under 35 U.S.C. § 102(e) as being anticipated by Khosla *et al.* (USPN 5,712,146) (see IDS). The instant claims are drawn to yeast cells containing vectors encoding a selectable marker and an expression system for a functional modular PKS and methods of expressing the PKS protein.

Khosla *et al.* (USPN 5,712,146) teach a transformation of the pCK7 plasmid containing the *eryAI*, *eryAII*, and *eryAIII* genes and several selectable markers into *Streptomyces coelicolor* CH999 cells to express the erythromycin polyketide synthase (PKS) and, in turn, produce the polyketide product, 6dEB (see column 42, lines 21-40); a promoter operable in yeast is inherent in the expression plasmid since a PKS product was obtained. Also, the *ery* genes code for ketosynthase, acyl transferase, and acyl carrier protein PKS activities of the type I PKS producing erythromycin (see column 19, lines 1-7).

28. Claims 35-36 and 38 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gramajo *et al.* (see IDS). The instant claims are drawn to *E. coli* cells containing vectors encoding a selectable marker and an expression system for a functional aromatic PKS and methods of expressing the PKS protein.

Gramajo *et al.* teach the pT7-7 vector which comprises an ampicillin resistance selectable marker, the T7 gene 10 promoter (see page 6476, left column, first "MATERIALS" paragraph), and ORFs 1, 2, and 3 of the aromatic, type II polyketide synthase (PKS) gene producing tetracenomycin which ORFs code for ketosynthase and acyl carrier protein activities (see page 6481, left column, first full paragraph). Gramajo *et al.* also teach the transformation of this vector into *E. coli* host cells and the culturing of said cells to promote expression (see page 6481, left column, first full paragraph).

29. Claims 35-36 and 38 are rejected under 35 U.S.C. § 102(b) as being anticipated by Roberts *et al.* (see IDS). The instant claims are drawn to *E. coli* cells containing vectors encoding a selectable marker and an expression system for a functional modular PKS and methods of expressing the PKS protein.

Roberts *et al.* teach the pT7-7 vector which comprises a T7-specific promoter and the *eryAIII* gene of the modular, type I polyketide synthase (PKS) producing erythromycin which gene codes for ketosynthase, acyl transferase, and acyl carrier protein activities, said vector being transformed into *E. coli* for expression (see page 308, right column, first paragraph). A selection marker is inherent in the expression plasmid for selection after transformation since selection of transformed cells cannot be performed in the absence of a selectable marker and post-transformation selection is essential to an effective transformation

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

30. Claims 1-2 and 5 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lambalot *et al.* (1995) (see IDS) in view of Shen *et al.* (1993) (see IDS). The instant claims are drawn to host cells comprising an expression system for an aromatic PKS and an expression system for a holo ACP synthase.

Lambalot *et al.* (1995) teach the *E. coli* gene *dpj*, later called *acpS,* and its gene product, ACPS (a holo-acyl carrier protein synthase), which product "transfers the 4'-phosphopantetheine (4'-PP) moiety from coenzyme A ... to ... acyl carrier protein (ACP) in *Escherichia coli*" for activation of an ACP in fatty acid biosynthesis (see Abstract and first paragraph of introduction, page 24658); this *dpj* gene is isolated on the plasmid pDPJ (see page 24659, right column, third full paragraph). Lambalot *et al.* (1995) also teach that ACPS "will assist in the heterologous overproduction of appropriately modified 4'-PP requiring enzymes, such as ... TcmM", the ACP of an aromatic, type II polyketide synthase (PKS) which synthesizes tetracenomycin in *Streptomyces glaucescens* (see page 24661, last paragraph). While Lambalot *et al.* (1995) teach the overproduction of TcmM (in holo-form in the presence of ACPS) in combination with the heterologous production of the holo ACP synthase, ACPS, in *E. coli*, which host cells, in unmodified form, do not produce polyketides, Lambalot *et al.* (1995) do not teach the heterologous production of a minimal type II PKS which, in addition to an ACP, contains a ketosynthase/acyl transferase (KS/AT) region and a chain-length factor (CLF).

Shen *et al.* teach the expression of the *tcmJKLMN* genes in a *tcmGHIJKLMNO* null background (see Abstract); *tcmJKLMN* genes encode a minimal type II PKS (KS/AT, ACP, and CLF domains) that produces tetracenomycin (see pages 1535-6, bridging paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a host cell containing ACPS and the *tcmJKLMN* genes for heterologous production, particularly on separate vectors since both vectors are found separately in each reference, of tetracenomycin in *E. coli* because Lambalot *et al.* (1995) indicate that such

combinations will "greatly facilitate mechanistic studies of acyl activating enzymes in ... polyketide ... biosynthesis" (see page 24661, last paragraph).

The Examiner notes that this rejection is limited to the use of ACPS (the *E. coli*-derived holo ACP synthase - a phosphopantetheinylating enzyme) and aromatic, type II PKS genes expressed together in either *E. coli* or *Streptomyces*.

31. Claim 6 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Lambalot *et al.* (1995) (see IDS) in view of Shen *et al.* (1993) (see IDS) and in view of Bierman *et al.* (see IDS). The instant claims are drawn to host cells comprising an expression system for an aromatic PKS and an expression system for a holo ACP synthase, wherein at least one of said expression systems is integrated into the host cell's chromosome.

Lambalot *et al.* (1995) and Shen *et al.* (1993) teach as described above. Lambalot *et al.* (1995) and Shen *et al.* (1993) do not teach the use of integrating vectors.

Bierman *et al.* teach several vectors useful for the integration of a gene of choice into the host cell chromosome via homologous recombination (see Abstract and page 44, Table I).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use such integrating vectors, in addition to the teachings of Lambalot *et al.* (1995) and Shen *et al.* (1993) as described above, because "introduction of DNA by conjugal transfer provided an alternative and easier method" which can create "gene disruptions and gene replacements within" PKS gene clusters (see Bierman *et al.*, page 47, left column, first full paragraph and bridging paragraph).

The Examiner notes that this rejection is limited to the use of ACPS (the *E. coli*-derived holo ACP synthase - a phosphopantetheinylating enzyme) and aromatic, type II PKS genes expressed together in either *E. coli* or *Streptomyces*.

32. Claims 8, 9, 11, and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Bierman *et al.* (see IDS). The instant claims are drawn to actinomycete host cells having (1) at least three vectors, each vector comprising a portion of an aromatic PKS expression system or (2) at least two vectors, each vector comprising a module of a modular PKS expression system; wherein at least one of the vector is integrated into the host cell's chromosome.

Khosla *et al.* (USPN 5,712,146) teach as described above in the rejection under 35 U.S.C. § 102(e) of the instant claims. Khosla *et al.* (USPN 5,712,146) do not teach the option of using modified chromosomes that can result from plasmid integration.

Bierman *et al.* teach several vectors useful for the integration of a gene of choice into the host cell chromosome via homologous recombination (see Abstract and page 44, Table I).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use such integrating vectors, in addition to the teachings of Khosla *et al.* as described above, because "introduction of DNA by conjugal transfer provided an alternative and easier method" which can create "gene disruptions and gene replacements within" PKS gene clusters (see page 47, left column, first full paragraph and bridging paragraph).

33. Claims 13 and 14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Oliynyk *et al.* (see IDS). The instant claims are

drawn to host cells having at least two vectors, each vector comprising a module of a modular PKS expression system from a PKS of different origin.

Khosla *et al.* (USPN 5,712,146) teach as described above.

Khosla *et al.* (USPN 5,712,146) further teach the various active sites of a modular polyketide synthase (PKS) gene as being ketosynthase (KS), acyl transferase (AT), and acyl carrier protein (ACP) active sites "as well as a subset of reductive active sites (ketoreductase (KR), dehydratase (DH), enoyl reductase (ER))" in addition to the "thioesterase (TE) [active site] encoded at the end of [a] module to catalyze lactone formation" (see column 19, lines 14-20). Khosla *et al.* (USPN 5,712,146) also teach that "the combinatorial potential within these [modular] multienzyme systems could be considerably greater than that for aromatic PKSs" (see column 25, lines 28-30). While Khosla *et al.* (USPN 5,712,146) teach host cells containing vectors for hybrid aromatic PKSs (see column 33, EXAMPLE 4), Khosla *et al.* (USPN 5,712,146) teach no such hybrid PKSs for modular PKSs.

Oliynyk *et al.* teach a host cell containing a modular hybrid PKS resulting from the "specific replacement of the entire ...AT1 domain in DEBS1-TE [*eryAI* fused to the TE domain of the *ery* gene cluster] with its ... counterpart from module 2 of the rapamycin-producing PKS" (see page 835, left column, first full paragraph).

At the time the invention was made, one of ordinary skill in the art would have been motivated to combine the above references because polyketides "exhibit an impressive range of antibiotic, anticancer, anti-parasite and immunosuppressant activities" and "considerable interest has developed in the possibility of generating hybrid polyketides by suitable combination of

activities from different natural polyketide synthases" (see page 833, left column, first paragraph and right column, last paragraph).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

34. Claims 1, 3, and 30-39 are rejected under the judicially created doctrine of nonstatutory, obviousness-type double patenting as being unpatentable over claims 1, 3, 27, 28, 30-32, and 40-43 of U.S. Patent No. 6,033,883. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the claims of U.S. Patent No. 6,033,883 represent a species of the generically claimed subject matter of claims in the instant application. The claims in U.S. Patent No. 6,033,883 have the requirement that the nucleotide sequences of the holo ACP synthase and the entire PKS be fused, which stipulation is absent in the claims of the instant application. Thus, the claims in U.S. Patent No. 6,033,883 are to a particular species of the genus in the claims of the instant application.

35. Claim 2 is rejected under the judicially created doctrine of nonstatutory, obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 6,033,883. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of claim 2 of U.S. Patent No. 6,033,883 represents a species of the generically claimed subject matter of claim 2 in the instant application. Claim 2 in U.S. Patent No. 6,033,883 has two requirements: 1) that the nucleotide sequences of the holo ACP synthase and the entire PKS be fused and 2) that the PKS must be fungal; these stipulations are absent in claim 2 of the instant application. Thus, claim 2 in U.S. Patent No. 6,033,883 is to a particular species of the genus in claim 2 of the instant application.

36. Claim 4 is rejected under the judicially created doctrine of nonstatutory, obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,033,883. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of claim 1 of U.S. Patent No. 6,033,883 represents a species of the generically claimed subject matter of claim 4 in the instant application. Claim 1 in U.S. Patent No. 6,033,883 stipulates that the nucleotide sequences of the holo ACP synthase and the entire PKS be fused while claim 4 of the instant application requires fusion, but only to "at least a portion of said minimal PKS" and not the entire PKS. Thus, claim 1 in U.S. Patent No. 6,033,883 is to a particular species of the genus in claim 4 of the instant application.

37. Claims 8, 9, 12-14, and 16 are rejected under the judicially created doctrine of nonstatutory, obviousness-type double patenting as being unpatentable over claims 5, 7, 9 17, and 19 of U.S. Patent No. 6,033,883. Although the conflicting claims are not identical, they are

not patentably distinct from each other because the subject matter of claims 5, 7, 9 17, and 19 of U.S. Patent No. 6,033,883 represents a species of the generically claimed subject matter of claims 8, 9, 12-14, and 16 in the instant application. Claim 5, a) and b), in U.S. Patent No. 6,033,883 use the same claim language as claim 8, a) and b), in the instant application; however, claim 5 in U.S. Patent No. 6,033,883 also stipulates a PKS comprising KS, AT, and ACP domains while being encoded by less than a complete open reading frame. This PKS is, in fact, equivalent to the modular PKS in claim 8 of the instant application that is a minimal PKS and is encoded by less than a complete open reading frame. Thus, the only remaining difference between claim 5 of U.S. Patent No. 6,033,883 and claim 8 of the instant application is the inclusion of aromatic PKSs in the instant application. Therefore, claim 5 of U.S. Patent No. 6,033,883 is to a species of the genus in claim 8 of the instant application. The same reasoning follows for claims 9, 12-14, and 16 of the instant application and claims 7, 9, 9, 17, and 19 of U.S. Patent No. 6,033,883.

38. Claims 1-3, 5, 6, 16, 32, 34, 37, and 38 are rejected under the judicially created doctrine of nonstatutory, obviousness-type double patenting as being unpatentable over claims 1-5, 13, 8, 9, 11, and 12, respectively of U.S. Patent No. 6,258,566. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the claims of U.S. Patent No. 6,258,566 represent a species of the generically claimed subject matter of claims in the instant application. The claims in U.S. Patent No. 6,258,566 have the requirement that the nucleotide sequences of the holo ACP synthase by particular holo ACP synthases. Thus, the claims in U.S. Patent No. 6,258,566 are to a particular species of the genus in the claims of the instant application.

Conclusion

39. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
January 24, 2003